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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,877	06/20/2001	Henricus Petrus Joseph Te Riele	065691-0230	3654

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,877	TE RIELE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,27,28 and 33-49* is/are pending in the application.

4a) Of the above claim(s) *34-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,27,28 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed June 20, 2001 is a continuation in part of 09/147,712, filed February 23, 1999, now abandoned, which is a national stage filing of PCT/EP95/02980, filed July 26, 1995.

Applicants' amendment filed October 14, 2004, has been received and entered. Claim 27 has been amended. Claims 1-23, 25, 26, 29-32 have been canceled. Claims 24, 27, 28, 33-49 are pending.

Election/Restriction

Applicant's election with traverse of Group I, in Paper No. 13 was acknowledged. No new arguments are provided in Applicants' instant amendment, Therefore, the requirement is maintained for the reasons of record and still deemed proper.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 24, 27, 28, 33-49 are pending. Claims 34-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 24, 27, 28 and 33 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 33 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants note the requirements for making a deposit and that an acceptable deposit will be made before the payment of the issue fee. See Applicants amendment, pages 6-7. Applicants arguments have been fully considered, but not found persuasive.

Even if a proper deposit were made, for example if the deposits are made under the terms of the Budapest Treaty, **then** an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

No such affidavit nor statements have been made by Applicants. Applicants arguments and request are noted, however Applicants have not complied with the requirements for a proper deposit. Therefore, the rejection is maintained for the reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27 and 28 rejected under 35 U.S.C. 112, second paragraph, is withdrawn.

The amendment to the claims has obviated the basis of the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 27, 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Varlet *et al.*, Genbank accession number X81143, and Berns *et al.* (US Patent 5,789,215 or WO 93/04169) in view of Orth et al. (PNAS, 1994).

Applicant summarize the requirements for making a proper rejection under 35 USC 103 (pages 7-8), summarize the teachings of the individual references and argue that Orth provides a teaching away because of the teaching that only genes with microsatellite sequences would be affected by MSH2, not an overall affect of miss-match repair (page 8). Berns does not remedy this deficiency because it provides only methods of generating a transgenic animal (page 9). See Applicants' arguments, pages 7-9. Applicants' arguments have been fully considered, but not found persuasive.

Initially, it is noted that Applicants do not argue that the reference fail to teach all the elements encompassed by the claim nor that there in not a reasonable expectation of success.

Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988).It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors.

In this case, at the time of filing the function of MSH2 were known and fairly well characterized in several species. As noted in the prior office action, Varlet *et al.* teaches that homologs of Msh2 were known for several species including the mammals mouse and human (summary in figure 1). Further, Varlet *et al.* summarize the prior art and teach that Msh2 in lower eukaryote was associated with mismatch repair. In higher eukaryotes, Varlet *et al.* summarizes that mutations and absence of the Msh2 gene in humans is associated with hereditary non-polyposis colorectal cancer (HPNCC), and the predisposition of a patient to tumor formation (pages 5723-4, bridging paragraph). The predisposition to tumor formation associated with the loss of Msh2 in tumors was consistent with the loss mismatch repair in *in vitro* systems where the biochemistry of Msh2 was previously analyzed and described in the

prior art (page 5723, first paragraph). To analyze homologs of Msh2 previously described in the art, Varlet *et al.* describe the isolation of the mouse Msh2 coding sequence (bridging pages 5724-5725) and indicate that the mouse sequence was deposited as X81143 (see Genbank listing). In characterizing the endogenous expression of Msh2 in the mouse Varlet *et al.* demonstrate a ubiquitous mRNA expression pattern throughout most of the tissues tested (figure 3). Varlet *et al.* note that the expression pattern in the mouse is consistent with replication, however in view of the limited spectrum of tumors in patients with hereditary non-polyposis colorectal cancer the tissue specific role of Msh2 'in HNPCC patients is surprising' (page 5727, top of first column). Varlet *et al.* propose several possible explanations for the observed results and indicate 'further study of the biochemistry (in Xenopus egg lysates) and of the genetics (in mouse) of mismatch repair will shed new light on its [Msh2] role in the maintenance of the integrity of eukaryotic genome, and in the development of cancer (page 5727, final paragraph).

Clearly the prior art recognized the MSH2 was generally associated with mismatch repair. Examiner acknowledges the teachings of Orth *et al.* noted by Applicants, however this does not teach away from the role of MSH2 known in the art at the time of filing. Again, Orth *et al.* teaches that in mammals, in particular humans, the characteristic of genetic instability in cell requires that both copies of MSH2 be disrupted. More specifically, Orth *et al.* teach that an individual can be heterozygous for a mutation of MSH2, however it is only as a consequence of the loss of both copies that a results in a phenotype characterized by genetic instability as seen in the resulting tumors as observed in ovarian cancer. Orth et al. is cited to demonstrate specifically the importance of having both copies of MSH2 deleted and its consequential affect on the genome of a cell. Varlet *et al.* was further cited to demonstrate that in the prior art that the

skilled artisan actively sought to affect and characterize the function of MSH2 in an *in vivo* context. Varlet *et al.* indicate that further research is required to address their hypothesis explaining the limited spectrum of tumor formation *in vivo* in patients with mutant Msh2 alleles, and provide the suggestion to use the mouse model however Varlet *et al.* do not provide the specific guidance to provide such a model system. At the time of filing transgenic mice were used to provide *in vivo* models of human diseases.

Examiner acknowledges that both references by Berns *et al.* teach a method of generating transgenic animals wherein a gene of interest is disrupted, however this was provided to demonstrate the methodology for generating an animal model were known and the suggestion of Varlet *et al.* could be accomplished with methods known at the time of filing. Moreover, it is noted that Varlet *et al.* specifically teach that further *in vivo* analysis of the role of Msh2 is required and that the study of the genetics in mice will provide further insight on the development of cancer, therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate animal model system wherein the specific Msh2 sequences disclosed by Varlet *et al.* are disrupted in the cells of mouse. Berns *et al.* provide the methodology to generate gene disruptions in embryonic stem cells through homologous recombination and provide guidance to for the generation of a transgenic mouse from said genetically modified embryonic stem cell.

Thus, contrary to Applicants arguments one having ordinary skill in the art would have been motivated to use the methods described by Berns *et al.* to disrupt the expression of the Msh2 gene because Varlet *et al.* teach that it is the absence of expression of the Msh2 gene that was associated with the mutant phenotype in cells and in tumors isolated from patients. Further,

by providing a mouse embryonic stem cell with the endogenous Msh2 gene expression disrupted using the methods of Berns *et al.*, a knock-out animal can be produced to test the hypothesis set forth by Varlet *et al.*

As summarized previously, there would have been a reasonable expectation of success to generate a mouse embryonic stem cell with a disrupted Msh2 gene using the methods of Berns *et al.* given the successful results demonstrated by Berns *et al.* for the Rb gene in the working examples and his teaching that other knock-out animals have been made using similar methodology.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach